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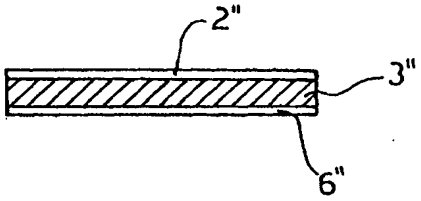
(54) Title: TRANSDERMAL PATCH AND TOPICAL COMPOSITIONS COMPRISING PROPYLNORAPOMORPHINE

(57) Abstract

Pharmaceutical composition comprising R(–)–propylnorapomorphine hydrochloride or S(+)–propylnorapomorphine hydrochloride and/or derivatives thereof, together with antioxidants, solubilizers and permeation activators to facilitate the passage of the active principle through the skin. The pharmaceutical composition is used in matrix (3, 3', 3") of a transdermal patch (1, 1', 1"), for the treatment of disorders of the Central Nervous System and in particular for the treatment of sexual impotence, hemicrania, Parkinson's disease and psychotic disorders. The release of the active principle can be modified by varying the concentrations of the solubilizers or of the permeation activators, or by providing a permeable membrane (4).



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TRANSDERMAL PATCH AND TOPICAL COMPOSITIONS COMPRISING PROPYLNORAPOMORPHINE

Description of the invention entitled:

"TRANSDERMAL PATCH AND PHARMACEUTICAL COMPOSITIONS COMPRISING R(-)-PROPYLNORAPOMORPHINE HYDROCHLORIDE AND/OR S(+)-PROPYLNORAPOMORPHINE HYDROCHLORIDE AND/OR DERIVATIVES THEREOF, IN THE TREATMENT OF SEXUAL IMPOTENCE, HEMICRANIA, PARKINSON'S DISEASE AND PSYCHOTIC DISORDERS"

Technical field

The present invention refers to the use of substances such as R(-)-propylnorapomorphine hydrochloride [hereinafter abbreviated to R(-)-NPA-HCl, or Compound (1)] and S(+)-propylnorapomorphine hydrochloride [S(+)-NPA-HCl, or Compound (2)] and the derivatives thereof, for the treatment of Parkinson's disease, hemicrania, sexual impotence, and psychotic disorders.

More particularly, the invention also concerns a "device" (transdermal patch) for the slow release of said substances through the skin.

Prior Art

Apomorphine (11B-13B) has been successfully used as a drug and, especially in the veterinary field, as an emetic. It has recently been found that apomorphine (abbreviated to APO), at suitable dosages, can have beneficial effects on patients with Parkinon's disease, while at lower dosages it is useful in the treatment of hemicrania, sexual impotence and psychotic disorders (4B, 5B, 6B, 7B).

In the abovementioned therapeutic indications APO is a powerful dopaminergic agonist drug, administered by the intravenous (i.v.), subcutaneous (s.c.), intramuscular (i.m.), rectal, sublingual or intranasal route. The substance is characterized by a rapid

absorption, correlated with a rapid attack (latent period about 15') and an equally rapid elimination (half-life about 33') (8B).

The molecule of apomorphine is unstable on exposure to air and to light, oxidizing rapidly. When exposed to air, in fact, preparations based on apomorphine change colour, turning green, thus giving rise to a product which can no longer be used clinically.

For this reason, in order to guarantee the patient the necessary pharmacological cover, with therapeutically effective blood levels that are sufficient and constant over 24 hours, a large number of daily administrations are needed, with limited doses, of the order of 1-5 mg/hour of active principle. Exceeding such a dose by even the slightest amount causes serious side effects, such as vomiting, depression of the central nervous system (CNS) and, in some cases, even death of the patient.

Recently the administration of apomorphine by continuous subcutaneous infusion, by means of small insulin pumps which should guarantee pharmacological cover with the hourly infusion of low doses, without causing side effects, has been proposed and carried out in medical practice. But even this alternative mode of administration is not without disadvantages: already with dosages of 2-5 mg/hour, there is a tendency that subcutaneous granulomas form around the infusion site, which require the suspension of the treatment. This is due to the fact that the drug is practically concentrated at one point: around the point of the needle.

Description of the invention

It is an object of the present invention to use a pharmaceutical composition based on R(-)-NPA-HCl (Compound (1)) or S(+)-NPA-HCl (Compound 2) and/or the derivatives thereof, which can be administered to the patient in therapeutically effective doses of

active principle, in a continuous manner, without causing the occurrence of serious side effects, such as vomiting and depression of the central nervous system (CNS), due to a high dosage of active principle, or else granulomas around the infusion site (when the dosage is lower), as found with the use of APO.

The activity of Compounds (1) and (2) is 10 times greater than that of APO, and in addition their toxicity is lower. In addition, the half-life is greater than that of APO. For this reason, when said compounds are given at suitable doses over 24 hours, effects which are rather more beneficial than those of APO are obtained.

Another object of the present invention is to produce a transdermal patch for the slow release of Compounds (1) and (2), and/or the derivatives thereof, hereinafter also called PATCH-TDSS (TDDS = Transdermal Drug Delivery System). The transdermal patch of the invention will guarantee a therapeutically effective level of Compounds (1) or (2) and/or the derivatives thereof (active principle) over 24 hours, without presenting the disadvantages of the traditional techniques.

This is because, as the patch is of relatively large dimensions (40 cm^2 for example), the active principle can permeate the epidermis through all the 40 cm^2 without any possibility of producing accumulation sites.

Moreover, the greater therapeutic activity allows the dosage to be reduced about 10 times. The greater solubility in water allows the release and index of permeation in vivo to be suitably modified by the addition of suitable permeation activators.

Brief description of the drawings

The present invention will be described in greater detail with reference to some of the preferred embodiments thereof shown in the appended drawings, in which:

Fig. 1 is a first type of transdermal patch, according to the invention, with a permeable membrane;

Fig. 2 is a second type of transdermal patch, according to the invention, without a permeable membrane;

Fig. 3 is a third type of transdermal patch, according to the invention, with an adhesive matrix;

Fig. 4 is a diagram of the permeation of Compound (1) in vitro on guinea-pig skin (accumulation);

Fig. 5 is a diagram of the permeation of Compound (1) in vitro on guinea-pig skin (flow per unit of time);

Fig. 6 is a diagram which shows the approximate curve representing human plasma levels at the times indicated (in hours (h)) relative to the active principle (1).

Preferred embodiments

Fig. 1 shows a first type of transdermal patch 1 which includes an impermeable support film 2 on which a matrix 3 is arranged. The active substance, (1), (2), and/or the derivatives thereof, is dissolved and/or dispersed in the matrix 3 which serves as a reservoir. The matrix 3, on the opposite side to the impermeable support 2, is covered by a membrane 4 permeable to the active substance, which regulates the cross-flow. This membrane may not be necessary if the degree of permeation of the active substance in the skin does not exceed the values which might cause side effects (see Figs. 2 and 3 where this membrane is not provided).

The degree of diffusion of the active substance will also depend on the permeation activators, solubilizers, etc. On the free side of the permeable membrane 4 there is a layer of a contact glue 5 (adhesive layer), protected by a release strip 6. During the use of the transdermal patch the release strip 6 is pulled off and the patch is positioned on the desired part of the patient's body, exerting slight pressure.

After a "start" phase the flow reaches a constant "saturation" value.

The release curves of the active substances (see Figs. 4, 5) and the plasma concentration based on a computerized model will be discussed below, with reference to the transdermal patch of Type III.

In the case of the patch 1' of Type II (Fig. 2), a matrix or "reservoir" 3, in which the active substance is dissolved and/or dispersed, is applied on the impermeable support film 2'. In the present case the membrane permeable to the active substance, which is used to modify the cross-flow, is missing. The matrix 3' therefore comes into direct contact with the epidermis. The glue 5' is located around the edge of the patch, like an adhesive ring. Everything is protected on the free side by a single release strip 6', which is removable, as for Type I.

The use of the "device" is as follows: the release strip 6' is pulled off and the device is positioned on the desired part of the patient's body, exerting slight pressure.

This solution (Type II) can be adopted in particular if the active principle interacts in an unwanted manner with the adhesive, as a result of which it is not possible to mix the adhesive 5' and the active principles in the matrix 3'.

Patch Type III is the one relating to the "drug in an adhesive matrix".

In this "device" the pharmacological dose is placed directly, dissolved or dispersed, into the glue, which thus also becomes a "reservoir" matrix 3" and which is arranged in a layer on a permeable support film 2". The adhesive matrix 3" is protected on one side by the support 2" (backing) and on the other by the release strip 6". The use of the device is as follows: the release strip 6" is pulled off and the device is positioned on the desired part of the patient's body, exerting slight pressure.

Depending on the particular application, the first, second or third type of patch will be used. It is obvious, however, that a person skilled in the art will be able to modify the shape and/or structure of the patch as he wishes, achieving the best result based on the therapy chosen and the site of application, or on other factors.

The three configurations shown in Figs. 1, 2 and 3, therefore, are examples and not limiting.

The differences in the structure and shape of the patch (rectangular or anatomical) may be due:

- to the interactions which may exist between the active principle, the glue (different types of adhesive can be used simultaneously), the support material, and other materials such as excipients, stabilizers, etc.;
- to better stability on the chosen site of application;
- to the dosage (the area of the patch must also increase for a higher dosage).

For purposes of illustration, the method of manufacture of the patch of Type III will be discussed in the following description,

and in addition the components of the pharmaceutical composition which constitutes the matrix will be indicated.

Then, three particular non-limiting examples of the pharmaceutical composition used to form the matrix of a Type III patch will be illustrated (Fig. 3). The Type III patch, containing a matrix made up of these three types of formulations, will then be "tested" on guinea-pig skin, to analyse the permeation of the active principle, both with regard to the accumulation of active principle over 48 hours (Fig. 4) and with regard to the flow (also over 48 hours, Fig. 5).

Method of manufacture of the transdermal patch of Type III

1. The active principle (1) or (2) or a derivative thereof is incorporated simultaneously with the other components (stabilizer, permeation activators, etc.) in the hot adhesive solution and homogenized by stirring, until the liquid adhesive matrix or "reservoir" is obtained;

2. the liquid matrix is cooled, and acquires a "stringy" consistency;

3. the process for layering of the adhesive matrix on the support is carried out using a layering machine which is continuously connected with a drying machine, in the following phases:

- the blade of a knife is mounted across the entire width of the conveyor belt of the layering machine on which the release strip is securely positioned;
- the "stringy" adhesive matrix is poured in front of the blade, which, as the conveyor belt advances, distributes a uniform layer (layering) of adhesive matrix on the release strip;
- the thickness of the layer is mainly determined by the distance between the edge of the knife blade and the release strip running beneath it;

- the release strip, carrying the adhesive matrix, rotates inside the drying machine, in which the adhesive matrix is solidified by evaporation of the solvent, which is achieved by gradually increasing the temperature and the "ventilation", as shown in the following Table I.

TABLE I

Drying phase	Time (in minutes)	T °C	Vent. (rpm)
1	15	40	700
2	20	55	1000
3	25	70	1200

The process described allows elimination of the solvent, preventing it from being occluded by the rapid formation of a surface crust.

When the adhesive matrix has dried, the support film (backing) is applied. This phase, called "lamination", ends the process.

The process is described in the literature (9B, 10B, 11B) and gives rise to a PATCH-TDDS in which the adhesive matrix remains protected both by the "backing" and by the removable release strip.

It is very important to use an adhesive which is inert and permeable to (1) or (2) and the derivatives thereof, and the adhesive properties of which (cohesion, adhesion and interlacing) are not adversely affected by the active principle itself and/or by excipients or any other material added.

Composition of the Type III PATCH-TDDS

Adhesive matrix: formulation

- active principle: (1) or (2) or derivatives thereof;
- antioxidant: sodium metabisulphite, EDTA disodium salt;

- solubilizing agent: a glycol;
- permeation activator: fatty acids;
- acrylic resin to improve the cohesive strength: cationic copolymers based on dimethylaminoethylmethacrylate and methacrylic esters;
- cellulose derivatives to improve the cohesive strength: ethylcellulose;
- surfactant: SDS (sodium dodecylsulphate);
- pressure contact adhesive: mixture of two adhesives, A and B, in which A is a non-self-bonding acrylic contact adhesive of medium molecular weight with a high interlacing index, with a skin irritation index of 0.20, classified as "minimally irritating", using 100% ethylacetate as solvent; and B is a self-bonding acrylic adhesive with a high molecular weight, with moderate interlacing, with a skin irritation index of 0, classified as "non-irritating", using a mixture of ethylacetate, isopropanol, hexane and toluene as solvent.

Release strip

The release strip is a polyester film laminated with silicone on one side (that opposite of the adhesive matrix). The thickness is approximately 125 µm.

"Backing"

The "backing" is a laminated polyester film which is clear and occlusive with a thermoweldable layer. The total thickness is approximately 51 µm.

Quantity of active principle

The quantity of (1) or (2) or derivatives thereof, expressed as (1) or (2), is 5% by weight of the adhesive matrix and corresponds to 5 mg/cm^2 in the PATCH-TDDS. The major part of the drug

is dispersed in the matrix. A minor part is dissolved in the matrix. The drug dispersed in the matrix acts as a "reservoir", while the drug available for release and permeation is the dissolved drug.

Three examples of the efficacy in application of the Type III transdermal patch based on (1) or (2) and/or derivatives thereof are now given.

Three batches of patches of differentiated formulation containing (1) or (2) and/or derivatives thereof were prepared for this purpose.

Using the in vitro cell permeation technique recommended by the FDA in the USA (1B, 2B, 3B), the following results were obtained, for example, with three different formulations given below, where Compound (1) was used as the active principle, i.e. the pharmacologically most active molecule:

Example A

Batch R(-)-NPA-HCl/A, with addition of permeation inducers:

1) Compound (1)	2.00%
2) Sodium metabisulphite	0.20%
3) Solubilizing agent	4.00%
4) Acrylic resin	29.00%
5) Fatty acid 1	3.20%
6) Fatty acid 2	1.60%
7) Pressure-sensitive adhesive	60.0%

Example B

Batch R(-)-NPA-HCl/B, with addition of permeation inducers, active principle dispersed in the matrix (reservoir) 4.5%, active principle dissolved in the matrix 0.5%.

1) Compound (1)	4.99%
2) Sodium metabisulphite	0.50%

3) EDTA 0.025%

4) Solubilizing agent 9.96%

5) Fatty acid 1 7.96%

6) Fatty acid 2 3.97%

7) Acrylic resin 1.99%

8) Cellulose derivative 0.25%

9) Surfactant 19.90%

10) Pressure-sensitive adhesive 50.455%

Example C

Batch R(-)-NPA-HCl/C, with addition of permeation inducers, active principle 0.5% in the matrix (all of the drug is dissolved):

1) Compound (1) 0.50%

2) Sodium metabisulphite 0.50%

3) EDTA 0.025%

4) Solubilizing agent 9.96%

5) Fatty acid 1 7.96%

6) Fatty acid 2 3.97%

7) Acrylic resin 1.99%

8) Cellulose derivative 0.25%

9) Surfactant 19.90%

10) Pressure-sensitive adhesive 50.945%

Experimental results

The in vitro permeation study with guinea-pig skin, carried out in accordance with the stated procedures, showed a permeation rate equal to the values given in Fig. 4 (total quantity) and in Fig. 5 (flow), for the three examples A, B and C, at the different times.

It can be observed that in the case of Example C the values are almost zero, i.e. all the black squares are virtually located on the axis of abscissae (time, in hours).

This demonstrates that a quantity of 0.5% of active principle dissolved in the matrix, in the absence of a certain quantity of dispersed active principle, does not produce an appreciable permeation of the active principle through the skin such as to permit the use envisaged.

It will therefore be necessary to disperse a certain quantity of active principle in the matrix, in such a way as to produce a concentration gradient which facilitates the diffusion of the active principle, as well as constituting a "reservoir", in order to obtain a slow release.

On processing the in vitro permeation data reported above with one of the most appropriate pharmacokinetic models for the transdermal administration of the drugs (10B, 11B), and considering a patch of 40 cm^2 (5 x 8 cm) with the following constants:

molecular weight of propylnorapomorphine hydrochloride	331.8
water/alcohol distribution coefficient	0.0005
half-life	45
distribution volume	132

the approximate curve shown in Fig. 6 is obtained, representing the human plasma levels at the times indicated, in the case of application of a single Batch NPA/B patch (ordinate: unit ng/ml; abscissa: time in hours).

From Figs. 4 to 6, it is possible to conclude that the skin permeability of Compound (1) is in itself sufficient and modifiable upwards and downwards using different permeation activators such as fatty acids or alcohols.

All the in vitro permeation studies were carried out using models which use guinea-pig skin, which we know has a permeability

comparable to human skin and gives more reproducible results than the latter.

The chemical stability of Compound (1) in the formulation of the patch is achieved by the addition of an antioxidant (sodium metabisulphite) and is demonstrated with an accelerated stability test of 15 days at 40°C and 75% RH (relative humidity).

The surfactant (SDS) is added with the aim of solubilizing a greater quantity of Compound (1), as only the solubilized substance (1) is available to be released and permeated. The patches have also exhibited good physicochemical properties which can be optimized by persons skilled in the art with regard to adhesivity at the site of application and tolerability by the subject under treatment without modifying the permeation rate of the active principle.

As has been said previously, the most appropriate configuration of the transdermal patch varies depending on circumstances. The Type III patch, for example, can be cut from a tape of greater dimensions, to obtain a transdermal patch of the appropriate size for the site of application.

The Type II patch, on the other hand, will already have to have the final dimensions, and cannot be cut, as the matrix 3' is not adhesive and the glue is limited to the annular region 5'.

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CLAIMS

1. Pharmaceutical composition characterized by comprising R(-)-propylnorapomorphine hydrochloride and/or S(+)-propylnorapomorphine hydrochloride and/or derivatives thereof, in pharmaceutically acceptable and effective doses, and furthermore comprising stabilizers, solubilizers and permeation activators to facilitate the passage of the active principle through the skin.

2. Pharmaceutical composition according to Claim 1, characterized in that said derivatives of R(-)-propylnorapomorphine hydrochloride and of S(+)-propylnorapomorphine hydrochloride are salts or organic derivatives.

3. Pharmaceutical composition according to Claim 1, characterized in that said stabilizers are antioxidant substances.

4. Pharmaceutical composition according to Claim 1, characterized in that a glycol is used as solubilizer.

5. Pharmaceutical composition according to Claim 1, characterized in that fatty acids or alcohols are used as permeation activators.

6. Pharmaceutical composition according to Claim 3, characterized in that the antioxidant is sodium metabisulphite and EDTA.

7. Pharmaceutical composition according to any one of the preceding claims, additionally comprising a surfactant (SDS).

8. Pharmaceutical composition according to any one of the preceding claims, additionally comprising an acrylic resin to improve the cohesive strength, cellulose derivatives to improve the cohesive strength, and a mixture of pressure contact adhesives.

9. Transdermal patch (1; 1'; 1") characterized by comprising at least one support film called "backing" (2; 2'; 2"), an intermediate matrix (3; 3'; 3") containing the pharmaceutical composition referred to in Claims 1 to 8, and a protective release strip (6; 6'; 6").

10. Transdermal patch (1) according to Claim 9, characterized in that the matrix (3) does not include adhesives and on its lower side has a layer (4) made up of a permeable membrane.

11. Transdermal patch according to Claim 10, characterized in that the permeable membrane (4) which modifies the release of the active principle is itself made up of an adhesive layer for fixing on the skin.

12. Transdermal patch according to Claim 10, characterized in that the permeable membrane (4) is not adhesive and has underneath an adhesive layer (5) for fixing on the skin.

13. Transdermal patch (1') according to Claim 9, in which an adhesive layer (5') is applied on the sides of the matrix (3') not containing adhesives.

14. Transdermal patch (1") according to Claim 9, characterized by comprising an adhesive matrix (3") containing an acrylic resin and cellulose derivatives to improve the cohesive strength, as well as a mixture of pressure contact adhesives.

15. Use of the pharmaceutical composition referred to in Claims 1 to 8 to obtain a slow release of the active principle or principles through the skin, in the treatment of Parkison's disease, hemicrania, sexual impotence and psychotic disorders.

16. Use of a transdermal patch, as referred to in Claims 9 to 14, to obtain a slow release of the active principle or principles through the skin, in the treatment of Parkison's disease, hemicrania, sexual impotence and psychotic disorders.

17. Use of a transdermal patch according to Claim 16, in which part of the active principle is immediately available for permeation through the skin and another part thereof is dispersed in the matrix (3; 3'; 3") which acts as a "reservoir".

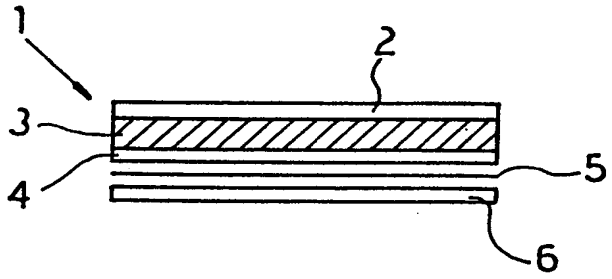

FIG. 1

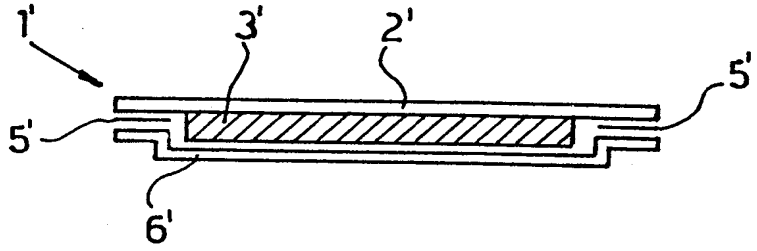

FIG. 2

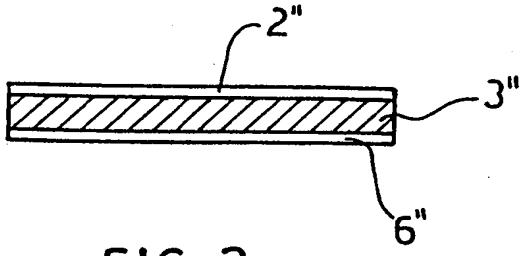

FIG. 3

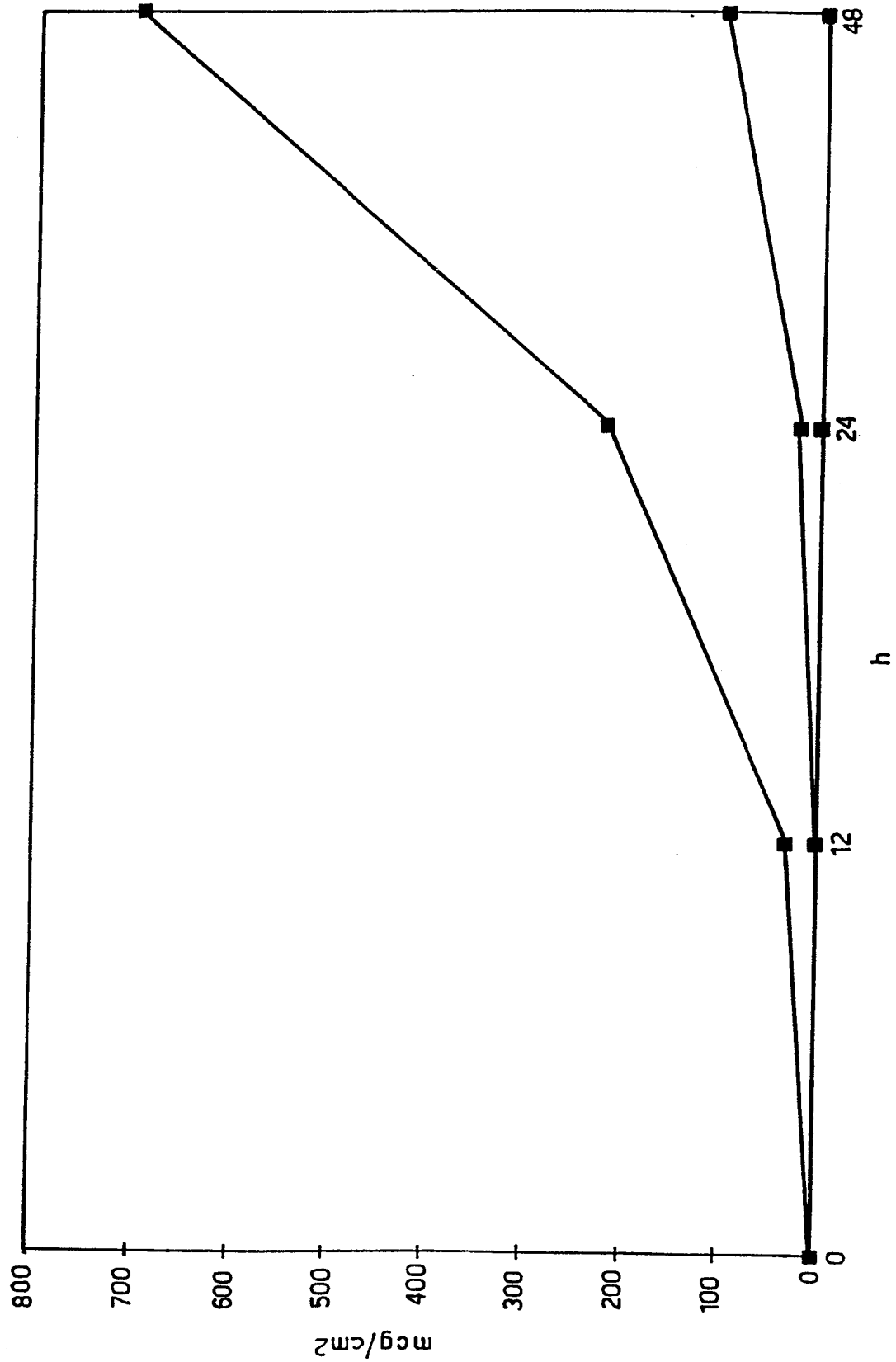
800
700
600
500
400
300
200
100
0
mcg/cm2
0
12
24
48
h
NPA/B
NPA/A
NPA/C

FIG. 4

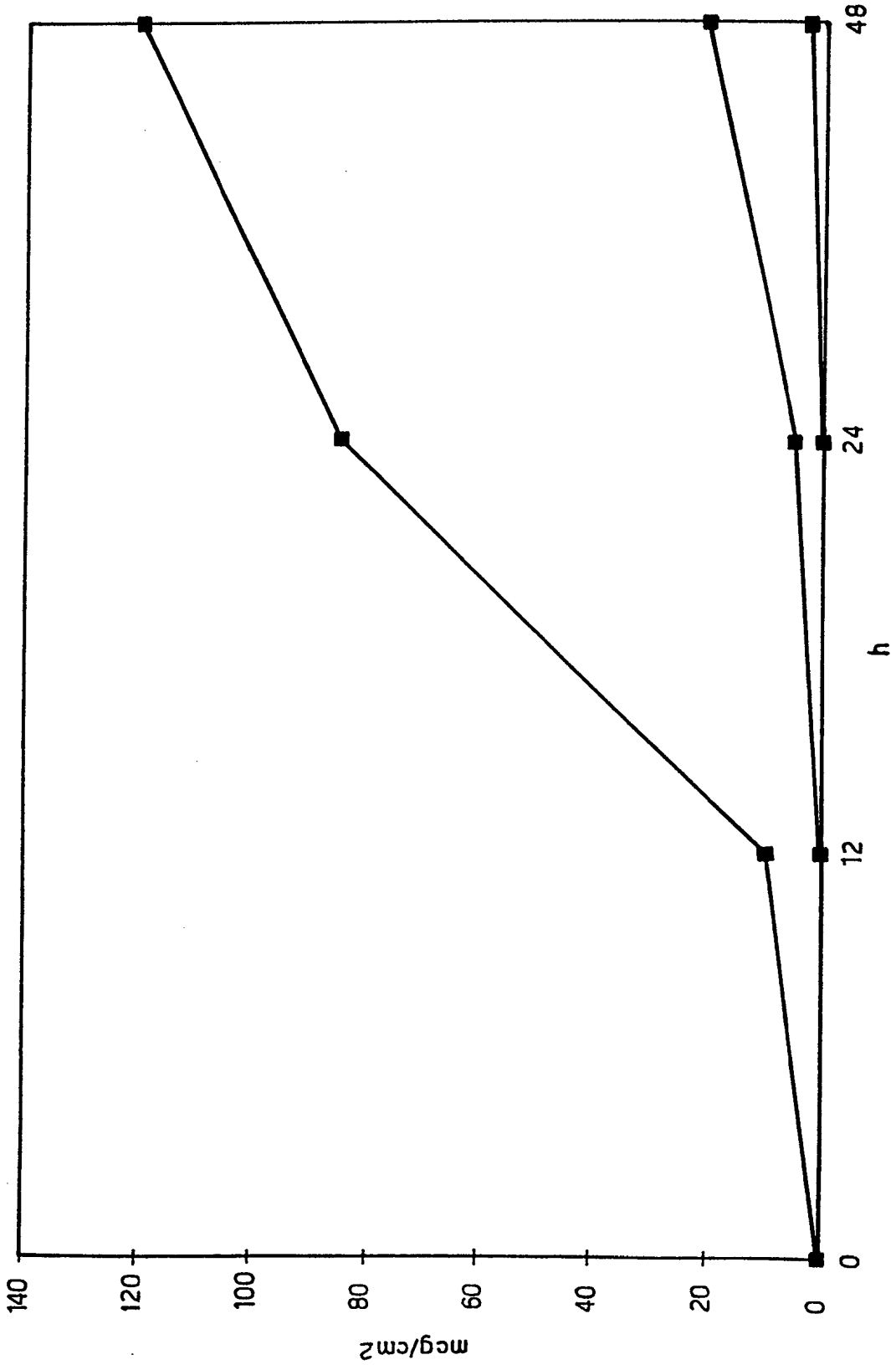

FIG. 5

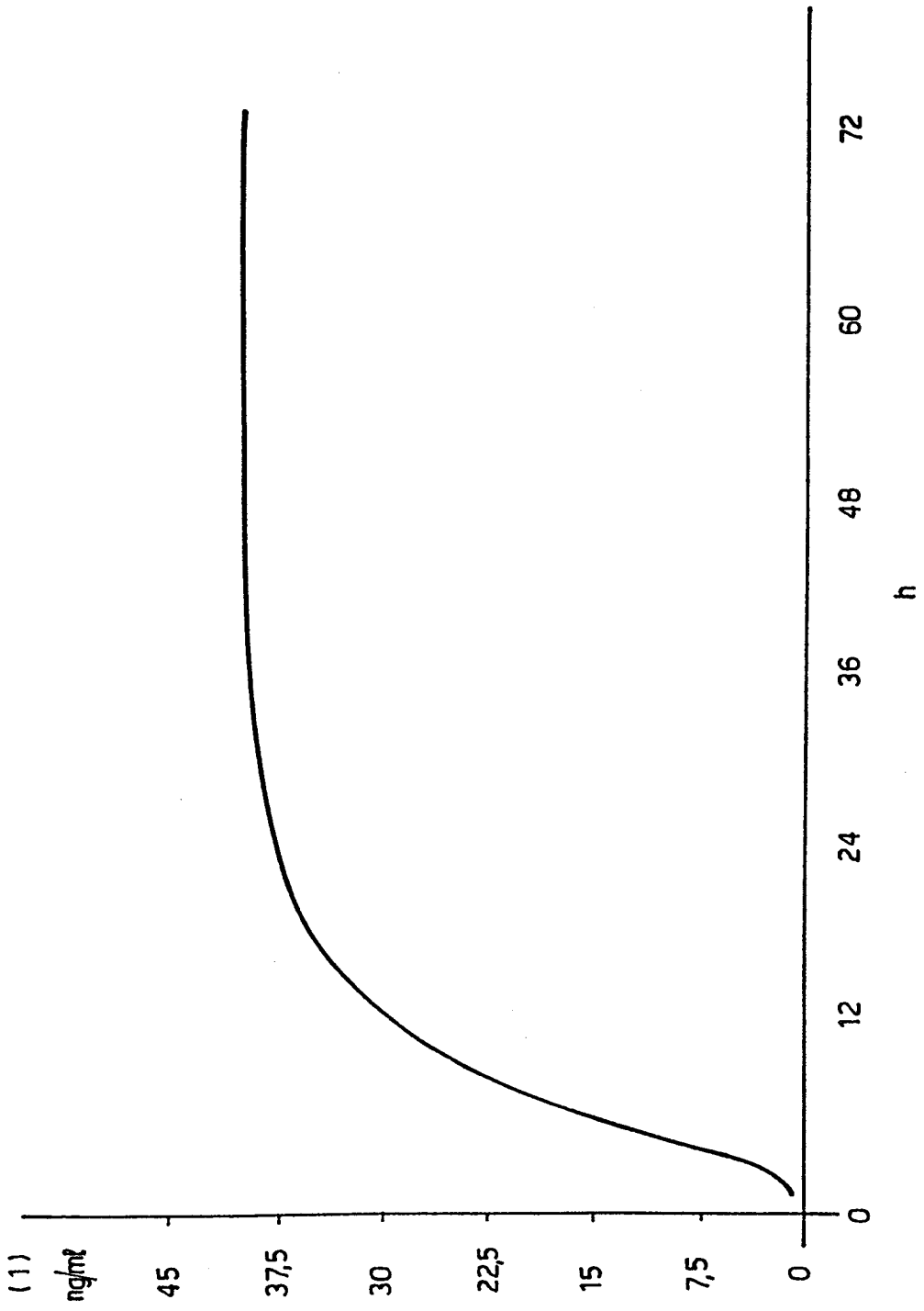

FIG. 6

INTERNATIONAL SEARCH REPORT

Interr onal Application No
PC /IE 99/00066

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K9/70 A61K31/485 A61P25/00 A61P15/10

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	ATKINSON ARTHUR D., ET AL.: "Emetic Actvity of N-substituted Norapomorphines" JOURNAL OF MEDICINAL CHEMISTRY, vol. 18, no. 10, 1975, pages 1000-1003, XP002118113 ISSN 0022-2623 page 1000, left-hand column, line 61 -right-hand column, line 51; table 1 page 1002, left-hand column, line 37 -right-hand column, line 8 ---	
A	US 4 126 616 A (HINSHAW WILLIAM BANKS ET AL) 21 November 1978 (1978-11-21) column 1, line 23 - line 63 column 4, line 4 - line 13 ---	
	-/--	

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
8 October 1999	21/10/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Epskamp, S

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Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/IE 99/00066

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	FR 2 732 896 A (PROGRAPHARM LAB) 18 October 1996 (1996-10-18) claims; figure 1	

2

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IE 99/00066

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although claims 15-17 are directed to a method of treatment of the human body, the search has been carried out and based on the alleged effects of the composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

formation on patent family members

International Application No
PCT/IE 99/00066

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 4126616 A	21-11-1978	NONE	
FR 2732896 A	18-10-1996	NONE	